Curr Allergy Asthma Rep
DOI 10.1007/s11882-013-0362-z

IMMUNOTHERAPY (L COX, SECTION EDITOR)

Allergen Immunotherapy Extract Treatment Set Preparation: Making a Safer and Higher Quality Product for Patients

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Abstract The best possible allergen immunotherapy clinical outcomes require the provision of high quality and safe allergen immunotherapy extract preparations. Evolving national guidelines and regulatory bodies have devoted special attention to the safe compounding of sterile products, including allergen extracts. It is incumbent upon allergists preparing extract treatment sets for patients to be familiar with and adopt training, procedures and safety measures that lead to standardized high quality products. Preparers and supervisors must maintain ongoing competency in aseptic technique and prescribing principles, such as probable effective dose ranges, allergen cross-reactivity, and separation of high protease-containing extracts from susceptible extracts. Accordingly, knowledge and application of vial labeling, diluent selection, standard operating procedures, mixing log documentation, and mixing condition principles are a necessity. Although there have been no instances of infectious complications from allergen immunotherapy in a century of clinical practice, continued vigilance in the use of measures that ensure extract sterility is paramount. A review of allergen immunotherapy preparation recommendations and best practices based on published national guidelines is presented. Further study of preparation measures and prescribing principles will continue to advance the practice of allergen immunotherapy and offer opportunities for refinement of current recommendations.

Keywords Allergen immunotherapy · Extract · Practice parameter · USP 797 · Compounded sterile product · Diluent · Preparation · Safety

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Published online: 25 July 2013

Introduction

Allergen immunotherapy (AIT) has been used in the beneficial treatment of patients for over 100 years. Recent advances in the practice of AIT have significantly improved AIT quality and clinical outcomes as a result of applying scientific study to a once anecdotal and apprenticeship-based clinical practice (Table 1).

There is a progressive mandate to further standardize AIT clinical practice in a manner that optimizes AIT quality and patient safety. Several published guidelines and reference manuals are available to preparers of AIT extracts including: allergen immunotherapy: a third practice parameter update [1]; allergen extract manufacturer preparation manuals, Allergen Immunotherapy Extract Preparation Manual [2]; and United States Pharmacopeia's General Chapter 797 (USP 797) [3]. The AIT practice parameter is now published as a third update by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology (JCAAI). The Allergen Immunotherapy Extract Preparation Manual is published as a chapter in the AAAAI Practice Management Resource Guide 2012 edition.

USP 797 was originally published in 2004 and revised in 2007. USP 797 describes standards for all compounded sterile products (CSP), including biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals. AIT extracts are thus by definition, CSPs. It was immediately recognized by allergists that AIT extracts that had been prepared safely for decades should be exempted from the application of rigid requirements previously referred to pharmacy preparation of products such as intravenous antimicrobials. Allergists and the JCAAI provided feedback that requirements such as multi-dose vial expiration labeling and use of mechanical ventilation hoods were prohibitive for the provision of the

Table 1 Allergen immunotherapy extract preparation practice parameter recommendations

Preparer qualifications	Storage
• Task training, written test. media fill test	• 4–8 °C in designated refrigerator (no food)
• Antiseptic hand and surface disinfecting	Prescribed route
• Identify, measure, and mix ingredients	• Subcutaneous according package insert or alternate route if accepted standards of clinical practice
• Training: RN, LPN, medical assistant, technician, physician, advanced practice nurse, other	
Physician responsibility	Aseptic technique
• Training and expertise in AIT	• Designate specific site with low traffic
• Ensures personnel trained, meet requirements and use aseptic technique	• 70 % isopropanol (no dye, glycerin, etc.)
• Maintain documentation in file	• Wash hands to wrist (soap/water or 70 % isopropanol or both)
• General oversight and supervision	• Sanitize ampoule necks and stoppers
Extract bacteriostasis	• Avoid contact contaminations
• phenol ≥0.25 % or glycerin ≥20 %	• Inspect physical integrity at completion
Prepare according to manufacturer instructions	Labeling
	• Name, beyond use date
Potency and beyond-use dates	Mixing log
• Manufacturer and based on best data	• Name, extract, mixing date, beyond use date, lot numbers
Mixing extracts	Policy and procedure manual
• Based partially cross-reactivity	
• Separate high protease extracts	

(Modified from Cox et al. [1])

outpatient-based practice of AIT in the absence of any safety concerns in decades of clinical practice. USP 797 was subsequently revised again in 2008 and now includes a dedicated section on the preparation of allergen immunotherapy extracts [3].

Practices affiliated with hospitals accredited by the Joint Commission are often required to be compliant with the Allergen Immunotherapy practice parameters and/or USP 797 standards. Although private practices not affiliated with hospitals are not typically accredited based on adherence to published guidelines, incorporation of guideline principles is the current standard of care for AIT in the United States. There is indeed considerable overlap of recommendations and best practices among these published guidelines. This review will focus on those principles and best practices that contribute to the quality and safe preparation of AIT extract patient treatment sets.

AIT Prescribing Principles

It is important for preparers of AIT patient treatment sets to review each new and refill prescription for accuracy, and as an opportunity to optimize each prescription before it is filled. Optimal AIT prescribing principles include use of a standardized prescription form, use of adequate allergen doses, and, when mixing multiple allergens are necessary, use of combinations that optimize allergen stability. Details of these major AIT prescribing principles and best practices are reviewed elsewhere [1, 2, 4, 5].

Every AIT prescription whether electronic or paper based should contain several basic information items at a minimum [1]. These include date, contact information and two patient identifiers for patients, name and contact information for prescribing physician, name and dose for each included allergen, diluent volume and description, number and concentration of serial dilutions, starting dose and schedule for each vial, and schedule adjustment instructions for lateness and adverse reactions. Finally, any special measures such as pre-injection peak flow measurement for patients with asthma.

There are multiple publications that have contributed to our growing knowledge of AIT extract prescribing best practices [1, 2, 4, 5]. Controlled clinical trials have yielded results that have been used to identify probable effective dose ranges. The AIT practice parameter third update summarizes probable effective dose ranges for dust mite (500–2,000 AU), cat hair/pelt (1,000–4000 BAU), standardized grass (1,000–4,000 BAU), Bermuda grass (300–1,500 BAU), short ragweed (6–12 mcg), dog (15 mcg Can f 1)[1]. These cited dose ranges are extracted from several clinical trials and are expressed in terms of major allergen content or total extract potency units for each allergen. Of note, these complex studies employed understandably limited numbers of doses for allergen dose–response curves, and varied in duration and clinical endpoints. Endpoints included

medication and symptoms scores, as well as immunologic surrogates of host immunologic response such as allergen-specific IgG4 production and skin test reactivity suppression. It is noteworthy that, although these doses were effective in the studied populations, further study is needed to define more precise probable effective dose ranges and whether the range will vary by clinical indication of AIT.

Use of multiple extracts for polysensitized patients is more the rule than the exception in United States. It is critically important to prescribe allergen combinations that optimize stability over the duration of use of all treatment vials. Data from in vitro and in vivo studies document the protease activity content of certain allergen extracts [6–12]. Cockroach and mold allergen extracts are considered high protease containing extracts, while pet danders and dust mite are considered low protease-containing extracts. Mixing high protease-containing extracts has been demonstrated to reduce the potency of pollens. One exception may be short ragweed pollen where there is conflicting evidence regarding potency preservation when mixed with mold or cockroach extracts [1, 7, 8]. Pollen extracts are largely considered devoid of proteases, although low levels of protease activity can be detected in fresh pollen grains [9]. There is conflicting evidence regarding the effect of mixing low and high protease extracts together such as dust mite and molds. Although current guidelines recommend separating high protease-containing extracts in a separate combined vial, one recent study highlights the potential for potency loss when *Alternaria* mold extracts are mixed with other high protease-containing mold or cockroach extracts [1, 10]. The authors suggest that there may be a role for separating high protease-containing extracts from each other in addition to be separated from pollens and low protease-containing extracts.

Current recommendations include separating high protease-containing extracts from pollen extracts, but allow for the mixing together of high protease extracts [1, 4]. Although in some circumstances this may result in the need for an extra treatment vial set and additional injection, assurance of adequate potency and dosing is preferred. It is important to note that the bulk of stability data is in vitro and focused on the maintenance extract vial. There is little data to date demonstrating whether the observed in vitro reduced potency results in reduced AIT clinical efficacy. It is also important to recognize that the effect may be even more pronounced in serially diluted vials where the final concentration of glycerin may be reduced depending on the diluent selected. Glycerin at concentrations above 20 % has been demonstrated to inhibit the observed protease-mediated degradation of pollen extract potency by cockroach and mold extracts [8].

Another key principle in prescribing allergen extract is to consider the use of cross-reacting allergens in selecting extracts for a given patient. The allergen immunotherapy practice parameter third update strongly recommends that physicians prescribing immunotherapy do not sacrifice adequate volumes of extracts to achieve probable effective doses for the purpose of "squeezing" more allergens into a vial for heavily polysensitized patients [1]. Prescribers can take advantage of known cross-reactivity relationships among related allergens to achieve effective doses and lessen the number of antigens required for treatment. Aeroallergen cross-reactivity has been demonstrated in vitro using enzyme immunoassays and in vivo using skin test cross-reactivity for a wide variety of allergens [1, 5, 13, 14]. Most closely botanical-related pollens contain allergens that are cross-reactive. Northern pasture grasses are perhaps the most widely recognized cross-reactive group of allergens, while other grasses possess more unique allergens and should be included in extracts in addition to a northern grass. The cross-reactivity demonstrated using specific IgE for diagnostic assays also translates to AIT treatment. AIT with timothy grass has been suggested to be effective for concomitant allergy to other northern pasture grasses such as rye, orchard, and fescue [1, 5, 15–17]. On the other hand, cross-reactivity among tree pollens is less prevalent, but strong where it exists, such as within the birch family that includes alder, hazel, and hornbeam pollens. Although the ragweed and Chenopod–Amaranth families are each very closely related as botanical families, there is considerable heterogeneity among weed pollens in general. For arthropods, there is considerable cross-reactivity among dust mite species but much less so for cockroach species. Treating with allergens possessing unique antigens and representative allergens for cross-reactive groups of allergens is an effective means of providing AIT.

Preparer Qualifications and Training

In order to optimize patient safety when preparing allergen extracts, it is important to incorporate training and competency assessment recommendations from published guidelines when developing specific clinic policies and procedures for allergen extract preparation. These guidelines note that the physician is ultimately responsible for the allergen extracts produced and must maintain oversight over each step of the process. Policies and procedures should be developed to address all aspects of AIT extract preparation, supervision, and training. Physicians, advanced practice nurses, physician assistants, registered nurses, licensed practical/vocational nurses, medical technicians, and medical assistants or other qualified personnel identified to prepare allergen extracts should undergo a standardized training curriculum with initial and ongoing competencies. Specifically, all personnel involved in preparing extracts should be instructed on aseptic technique, including handwashing, disinfection of mixing surfaces, and all aspects of allergen extract preparation. AIT extract preparers should acquire a basic

knowledge of aerobiology, specific aeroallergen extracts, extract mixing, vial dilution and reconstitution, vial labeling, and extract expiration dating procedures. Preparers should be trained to complete mixing documentation and a mixing log, ideally in an electronic database. Each mixing log entry should include the mixing date, patient identifiers, names of individual extracts and manufacturer, lot numbers, and expiration dates. Trained personnel should also pass a written test such as the exam posted on the JCAAI website. Preparers should also perform and pass a media fill test at least annually to demonstrate continued competency in aseptic technique. The initial and ongoing competencies, results of the media fill test, and written test results should be documented and maintained in the individual's personnel file.

Allergen Immunotherapy Extract Vials, Diluents, and Labels

It is important that preparers of AIT extract patient treatment sets carefully select materials used to mix prescriptions. This includes the use of stock extracts from reliable manufacturers that produce quality assured products in full compliance with Food & Drug Administration lot release requirements.

Aeroallergen stock allergen extracts are commercially available in aqueous, alum-precipitated, or acetone-precipitated forms. Selection of standardized allergen extracts is always preferable to non-standardized extracts. Nineteen allergen extracts have been standardized to date: eight grasses, cat hair and pelt, two dust mite species, short ragweed, five Hymenoptera venoms and one Vespid venom mix. Standardization is based on assuring allergen concentrations fall within a prescribed range based on major allergen content or in vitro correlates of skin test reactivity. Use of standardized extracts and calculated probable effective doses of individual allergens enables preparers to provide high quality AIT treatment sets. However, it is also well recognized that use of nonstandardized extracts is often required to treat allergic triggers for which standardized extracts are not available.

Allergen extracts selected for treatment should also correlate with allergens used in diagnostic testing. This raises the interesting question of whether pollen extract mixes used in skin testing should also be used for AIT treatment. Although few studies have reported on the use of allergen mixes for combined testing and treatment in AIT, this is an accepted clinical practice [1].

Often overlooked is the selection of sterile diluents for use in mixing maintenance, and serial dilution vials of patient treatment sets. Excipients in diluents serve multiple functions such as bacteriostasis (phenol, high concentration glycerin) and allergenic protein structure stabilization (glycerin, serum albumin). Examples of diluents commonly used in aqueous AIT vial preparations to reach target vial volumes, after addition of selected stock allergen extracts or for serially diluted vials, include 0.4 % phenol-saline, 50 or 10 % glycerin-saline with 0.4 % phenol-saline, and 0.03 % human serum albumin-saline with 0.4 % phenol.

Product package inserts, immunotherapy practice parameters, and USP 797 describe the use of sufficient concentrations of preservatives to prevent bacterial contamination. At least 0.25 % of phenol or 20 % of glycerin is recommended for adequate bacteriostasis in final maintenance and dilution vials [1–3]. Grass and birch allergen extract potency loss has been observed when using phenol-saline alone without glycerin or serum albumin as early as 3 months. When human serum albumin was added to a 0.03 % final concentration, a protective effect was observed on the potency loss for up to the 12 months studied [12]. Although 50 % glycerin is the most common diluent used for stock allergen extracts, high concentration commonly cause pain and irritation at injection sites [18]. Therefore, glycerin-based diluents used for fill volumes or serial dilutions typically limit the glycerin content to 10–20 % and contain phenol as the bacteriostatic agent. Phenol-saline is the sole recommended diluent for alum-precipitated extract preparations.

It is imperative for safe AIT administration that all extract vials be clearly labeled to ensure the correct dose of the correct extract is administered to the patient. Guidelines recommend that all extract vials labels should contain two patient identifiers, expiration or beyond use date, and storage temperature. Labels should also either contain abbreviations or names of allergen content or be linked to a document that lists specific allergen content. The expiration dates of AIT extracts are based on several factors, including the number and properties of specific allergen constituents, the presence of stabilizers (e.g., human serum albumin or glycerin), concentration, presence of proteolytic enzymes, and volume of the storage vial.

Including the concentration of each vial in serially diluted treatment set vial labels is also recommended. Concentrations should be listed as volume to volume with the red maintenance vial labeled 1:1 v/v. Serial dilutions in the recommended color coding scheme are also labeled in v/v units: yellow (1:10 v/v), blue (1:100 v/v), green (1:1,000 v/v), and silver (1:10,000 v/v). Use of numbering systems beginning at "1" or "A" for the maintenance vial or of concentrations of allergens in each vial remain alternative label options. However, these options may be a source of confusion for healthcare personnel administering allergy injections, especially when considering the legacy method of labeling vials in reverse order and the plethora antigen potency concentration units involved. Regardless of which system is used, it is imperative that the system is used uniformly to avoid confusion and subsequent errors.

The stability and potency of AIT extracts are also influenced by storage temperature [11, 12, 19]. Extracts stored at higher temperatures (i.e., room temperature) tend to be less stable and can undergo a rapid deterioration in potency. Since many AIT prescriptions are individualized with different constituents mixed together, it is recommended that all AIT extract vials be labeled with expiration date of the earliest expiring constituent and all should be stored at 4 to 8 °C.

AIT Treatment Set Preparation

Table 2 outlines the basic steps in AIT treatment vial set preparation. AIT treatment vials should be prepared in accordance with stock extract manufacturer instructions and published guidelines. A critical component of preparation is the preservation of aseptic technique throughout the creation of these compounded sterile products. This includes handwashing, gloves, sanitizing surfaces and vials, and minimizing exposure of preparation materials to potential contaminants.

Typical AIT treatment set standard operating procedures begin with identifying and sanitizing an appropriate area for mixing. USP 797 and the AIT practice parameter third update do not require ventilation hoods for preparation. However, selection of a consistent mixing location free of distractions and limiting nearby exposures to high risk contamination activities or items (e.g., food, waste) is recommended. The location can be multi-purposed, but should be used exclusively for mixing during AIT vial preparation. Use of medication zone markings and other best practices are often used by AIT extract preparers to minimize the risk of distractions and errors. Mixing materials (vials, syringes, stock extracts, diluents, labels, etc.) are assembled prior to starting the mixing procedure. Personal protective equipment (gloves, eyewear, etc.) is worn throughout the procedure and serves as an additional barrier to vial contamination. Labels are applied to vials and possibly syringes if transfers are not completed directly after pulling from the stock vial in accordance with Joint Commission standards. Vial stoppers are sanitized, typically with isopropanol pads. Prescribed allergens and diluents are then transferred using aseptic technique to the red 1:1 v/v maintenance vial, either by immediate transfer or pulling all allergens for the vial followed by sequential addition to the maintenance vial. Initial AIT extract treatment sets usually include 3–4 ten-fold dilution vials to permit AIT initiation with a dilute starting dose. Dilute or lower concentration vials are then prepared by serial dilutions beginning with the newly mixed red maintenance 1:1 v/v vial. Serial dilutions reduce the potential for error or variation compared to pulling minute amounts from stock vials to mix each lower strength vial. Standard operating procedures also point out methods for documenting the mixing procedure. Examples include a mixing log or compiling individually documented filled prescriptions that have been annotated with the date, name of preparer, patient name, contact information, allergen name, manufacturer, and lot numbers of allergen extracts and diluents used for each patient treatment set. The rationale for this recommendation is the recognized need for timely identification of patients who may have received individual allergen extracts that have been recalled for any reason.

Another important component of the procedure is to maximize the use of quality checkpoints. Table 2 also describes several opportunities to minimize errors through the use of frequent quality checks during AIT treatment set preparation. Verifying that label content matches the prescription before and after mixing is just one example. Preparers should also ensure that label concentrations and vial color coding match. Similarly, preparers should verify that there is a consistent visible decline in vial liquid color progression from darkest for the maintenance vial to lightest for the most dilute vial when applicable to vials containing darker-colored stock extracts. A recognized best practice includes the use of buddy checks for some or all of these quality checks. Furthermore, new software and automation systems have been developed to contribute to quality extract preparation. Examples include prescribing and documentation software, as well as syringe plunger brackets verifying specific volumes. Further study is indeed needed to identify

Table 2 Allergen immunotherapy extract preparation basic procedure and quality checks

Standard operating procedure Basic steps	Potential quality checkpoints
Review prescription	Total volume, probable effective doses, high protease mixtures
Identify and prepare mixing location Use personal protective equipment Sanitize mixing surface	
Assemble mixing materials	Expiration date of stock materials, stock extracts to be used match prescribed allergens
Apply custom label to vials	Patient identifiers, vial expiration date not later than earliest expiration date of any stock extract, correct dilution label for vial concentration
Sanitize vial stoppers	
Prepare maintenance extract (sterile transfers from stock allergen and diluents vials)	Verify syringe contains correct volume and antigen as prescribed
Conduct serial dilutions (usually 10-fold)	Vial liquid color dilution of final treatment set when applicable
Final quality checkpoint	Label/vial concentration/ prescription match

which measures significantly contribute to enhanced quality of AIT extract preparation.

AIT Preparation Safety

Qualified personnel that participate in allergen extract mixing should follow safe hospital practices including use of personal protective equipment and proper use and disposal of needles. Adhering to the basic principles of aseptic technique requires compounding personnel to wear personal protective equipment. The risk of injury from accidental spills of allergen extract is very low, thus protective equipment measures are primarily introduced to decrease microbial contamination. Table 3 provides a comparison of recommended safety measures from various guidelines. This comparison identifies some minor differences between practice parameters and USP 797 recommendations that are dwarfed by the common focus on minimizing the risks of vial contamination and preparer contact or injury.

Accidental needlesticks are a common problem among health care workers including compounding personnel who regularly use sharp objects in the course of their daily work.

Table 3 Comparison of national guideline allergen immunotherapy extract preparation safety and contamination prevention recommendations

	AIT practice parameter	USP 797 AIT extracts	USP 797 low risk CSP[a]
No makeup/jewelry	Y	Y	Y
Hand washing	Y	Y	Y
Hair/facial covers	Y	Y	Y
Shoe covers	N	–	Y
Low shed gown	N	Y	Y
Sterile gloves	N[b]	Y	Y
Wear mask	Y	Y	Y
Negative pressure room	N	N	Y
Dedicated room/space	Y[c]	–	Y
Air monitoring	N	N	Y
Culture space/finger	N	N	Y
Media fill testing	Y	–	Y
Written testing	Y	–	Y

[a] Recommendations for low risk compounded sterile products in USP 797. AIT extract preparation was considered low risk sterile compounding (single sterile transfers) prior to publication of the 2008 USP 797 revision with the allergen extract section

[b] Whereas use of sterile gloves is not specifically addressed by the immunotherapy practice parameter third update, use of either sterile or nonsterile gloves should be considered

[c] Dedicated room or space does not necessarily refer to exclusive use of that space for mixing at all times. However, dedicated use during mixing is required.

(Data from Cox et al. [1] and US Pharmacopeial Convention [3])

A high degree of caution must always be taken when using sharp items. Needlesticks can be prevented by avoiding recapping of needles and proper disposal of used needles. The use of safety cap needles is not required when participating in allergen extract mixing, but this can assist in preventing injury to compounding personnel.

Only a few studies have reported the risk of contamination of allergen immunotherapy vials or infections in patients receiving AIT. Letz and colleagues in a retrospective study of more than 2,000 AIT vials cultured for possible contamination identified only a single contaminated vial [20]. Lay et al. evaluated the risk of patient infections over a 6-year period for vials prepared in an office clinic setting [21]. This retrospective review of AIT involving 272 patients and 26,795 injections revealed zero instances of skin or systemic infections or infectious symptoms from AIT injections. In another study, Lay and colleagues demonstrated that. whether vials were prepared in a ventilation hood or typical office setting, there was little risk of contamination [22]. One positive culture was observed in 217 hood-prepared vials compared to 2 of 320 positive cultures in office-prepared vials. It was unclear whether the contamination was derived from prepared vials or the culture process. One prospective trial of 136 consecutively prepared AIT vials that were used for AIT administration routinely to patients over a 3-month period also identified a low risk of contamination, 0–3.7 % [23]. Combined, these data illustrate that the contamination risk is indeed low for allergen extract preparation under routine office conditions and use when properly prepared using diluents and commercial stock allergenic extracts containing preservatives. To our knowledge, there have been no described incidences of patient infections resulting from AIT administration.

Conclusions

Providing high quality allergen immunotherapy extracts for patients requires paying close attention to adequate dosing, protease separation, and cross-reactive allergen prescribing principles. Personnel entrusted with allergen preparation should be adequately trained and periodically assessed for competence to include mastery of aseptic sterile transfers. Details of vial and diluent selection, label content, quality checks during preparation, and mixing documentation, must not be overlooked. Fortunately, preparers and supervising clinicians have access to multiple resources to assist in training, assessment, and general knowledge. These include published guidelines, extract preparation manuals, and specialty society conference presentations and workshops.

The recent meningitis outbreak associated with the compounding of injectable corticosteroid preparations highlights the need to place renewed emphasis on sterile compounding

practices. It is incumbent upon AIT extract treatment set preparers and supervisors to share and adopt best practices from evolving guidelines and published AIT studies. It is also immensely evident that there is a great deal of need for additional investigation of preparation measures to further advance the quality of AIT preparations. The study of allergen immunotherapy preparation procedures will potentially improve clinical outcomes. Results will enable an evidence-based approach to preparation training and procedure modifications that improve the quality of extracts produced and provide the opportunity to re-evaluate recommended measures not demonstrated to be of significant value.

Acknowledgments The authors wish to thank Dr. Linda Cox, Dr. Bryan Martin, Dr. Michael Blaiss, Ms. Susan Kosisky, the U.S. Army Centralized Allergen Extract Laboratory and the JCAAI for their dedication to allergen immunotherapy preparation guidance and content for this review, and Ms. Karen Nelson for editorial assistance.

The views expressed in this article are those of the authors and do not reflect the official policy of Walter Reed National Military Medical Center, the Department of Defense, or the U.S. Government.

Compliance with Ethics Guidelines

Conflict of Interest Michael R. Nelson has been a US Pharmacopeia representative and an FDA Allergenic Products Advisory Committee member.

Maureen M. Petersen, Wayne O. Wolverton, and Cecilia P. Mikita declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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